

Claims:

1. N- and C-terminally double truncated tau molecules, characterized by the following features ("type IA tau molecules"):
 - the molecules have at least the first 236 N-terminal amino acids and at least the last 45 C-terminal amino acids of the 4 repeat containing tau43 truncated,
 - the molecules are detectable in Alzheimer's diseased brain tissue whereas the molecules are not detectable in normal healthy brain tissue and
 - the molecules prevent normal tau protein from promoting microtubule assembly in an in vitro microtubule assembly assay,
 - said prevention of the promotion of microtubule assembly can be eliminated by specific inhibitory, neutralising monoclonal antibodies against said molecules in a microtubule assembly assay.
2. Type IA tau molecules according to claim 1, characterized in that they comprise an amino acid sequence selected from the group of SEQ ID NOS 1 to 3.
3. N- and C-terminally double truncated tau molecules, characterized by the following features ("type IB tau molecules"):
 - the molecules have at least the first 238 N-terminal amino acids and at least the last 40 C-terminal amino acids of the 4 repeat containing tau43 or the first 207 N-terminal amino acids and at least the last 50 C-terminal amino acids of the 3 repeat containing tau44 truncated ,
 - the molecules are detectable in Alzheimer's diseased brain tissue whereas the molecules are not detectable in normal healthy brain tissue and
 - the molecules do not prevent wild type tau from promoting microtubule assembly in an in vitro microtubule assembly assay.
4. Type IB tau molecules according to claim 3, characterized in that they comprise an amino acid sequence selected from the group of SEQ ID NOS 4 to 10.
5. N- and C-terminally double truncated tau molecules, characterized by the following features ("type IIA tau molecules"):

- the molecules have at least the first 68 N-terminal amino acids and at least the last 40 C-terminal amino acids of the 4 repeat containing tau43 or the first 68 N-terminal amino acids and at least the last 20 C-terminal amino acids of the 3 repeat containing tau44 truncated,
- the molecules are detectable in Alzheimer's diseased brain tissue, whereas the molecules are not detectable in normal healthy brain tissue,
- the molecules have a higher microtubule assembly promoting activity than wild type tau in an in vitro microtubule assembly assay,
- said microtubule assembly promoting activity can be eliminated by specific inhibitory, neutralising monoclonal antibodies against said molecules in a microtubule assembly assay and
- the pathologic activity of said molecules relies their binding to the microtubular network defined by the microtubule polymerisation promoting activity.

6. Type IIA tau molecules according to claim 5, characterized in that the comprise an amino acid sequence selected from the group of SEQ ID NOS 11 to 18.

7. N- and C-terminally double truncated tau molecules, characterized by the following features ("type IIB tau molecules"):

- the molecules have at least the first 68 N-terminal amino acids and at least the last 40 C-terminal amino acids of the 4 repeat containing tau43 or the first 68 N-terminal amino acids and at least the last 20 C-terminal amino acids of the 3 repeat containing tau44 truncated,
- the molecules are detectable in Alzheimer's diseased brain tissue, whereas the molecules are not detectable in normal healthy brain tissue,
- the molecules have a pathological microtubule assembly promoting activity different from wild type tau in an in vitro microtubule assembly assay.

8. Type IIB tau molecules according to claim 7, characterized in that the comprise an amino acid sequence selected from the group of SEQ ID NOS 19 and 20.

9. Method for the preparation of molecules according to any one of claims 1 to 8, characterized in by the following steps:

- a) construction of a recombinant prokaryotic expression plasmids carrying coding sequences for a double truncated tau molecule with deletions covering at least the first 236 and the last 40 amino acids or the first 68 and the last 20 amino acids or combinations thereof,
- b) growing said bacteria under conditions allowing expression of said N- and C-terminally double truncated tau molecule,
- c) collecting of bacteria, preferably by centrifugation,
- d) resuspending the bacterial pellet,
- e) sonicating said bacteria,
- f) fractionating said sonicated bacteria by gel filtration and
- g) monitoring the activity of the obtained fractions by a microtubule assembly assay thereby identifying the different activities of type I and type II tau molecules.

10. Method according to claim 9, characterized in that the truncations are defined as in any one of claims 1 to 8.

11. Method according to claim 9 or 10, characterized in that the microtubule assembly assay activity is defined as in any one of claims 1 to 8.

12. Method for the preparation of molecules according to any one of claims 1 to 8, characterized in by the following steps:

- a) providing Alzheimer's diseased brain tissue,
- b) homogenising said diseased brain tissue in a buffer, especially in Tris buffer,
- c) ammonium sulfate precipitation of said homogenized brain tissue,
- d) redissolving in PIPES buffer,
- e) fractionating said redissolved material by gel filtration and
- f) monitoring the activity of the obtained fractions by a microtubule assembly assay thereby identifying the different activities of type I and type II tau molecules.

13. Method according to claim 12, characterized in that the microtubule assembly assay activity is defined as in any one of claims 1 to 8.

14. Method for testing substances effective in disassembling a complex of a molecule according to claim 1 or 2 (type IA molecules) and tubulin, comprising the following steps:

- a) allowing the formation of protein complexes between type IA molecules and tubulin and
- b) incubating the protein complexes with a substance to be tested and identifying those substances which inhibit type IA molecules and/or allow the restoration of the microtubule assembly promoting capacity of wild type tau and normal function of microtubules.

15. Method for testing substances effective in inhibiting molecules according to claim 1 or 2 (type IA molecules) from initiating the formation of complexes with tubulin in a cellular system expressing wild type tau comprising the following steps:

- a) introducing a functional gene encoding a type IA molecule under the control of suitable regulatory regions into a cell expressing normal tau protein,
- b) allowing the formation of protein complexes between type IA molecules and tubulin molecules,
- c) applying the substance to be tested to the cells harboring said complexes and
- d) examining the effect of said substance on type IA biological activity as defined in claim 1.

16. Method for in vitro conversion of microtubules into a pathological state characterized by incubating wild type tau protein with type IIA according to claim 5 or 6 under physiological conditions which allow the interaction of said type IIA molecules with microtubules generating pathological microtubules.

17. Method for screening substances capable of neutralising the pathological effects of a type IIA molecules according to claims 5 or 6 for their property to eliminate and/or neutralize type IIA molecules and to restore physiological microtubule parameters and functions caused by type II molecules comprising the following steps:

- a) formation of pathological microtubules in the presence of type IIA molecules and tubulin according to claim 16,

- b) incubation of a mixture of the substance, type IIA and tubulin with the substance to be screened and
- c) examination of the result with respect to diminishing the formation of pathological microtubules caused by type IIA molecules.

18. Method for testing substances effective in inhibiting the in vivo activity of type IIA molecules according to claim 5 or 6 in promoting abnormal microtubule formation and function in a cellular system expressing type IIA molecules comprising the following steps:

- a) introducing a functional gene encoding type IIA molecules under the control of suitable regulatory regions into a cell expressing wild type tau,
- b) allowing the formation of complexes between type IIA tau molecules and microtubules, whereby said complexes are involved in the formation of pathological microtubules,
- c) applying the substance to be tested to the cells harboring said complexes and
- d) examining the effect of said substance on type IIA biological activity, especially on the modifications of the microtubule network and its associated functions.

19. Transgenic animal expressing a molecule according to any one of claims 1 to 8.

20. Use of a transgenic animal according to claim 19 as animal model for Alzheimer's disease, especially for screening and testing drugs for the treatment of Alzheimer's disease.

21. Vaccine comprising a molecule according to any one of claims 1 to 8, especially according to claims 1, 2, 5 or 6, and a pharmaceutically acceptable carrier, especially an adjuvant.

22. Inhibitor of the initiation of the formation of complexes of a molecule according to claim 1 or 2 with tubulin.

23. Inhibitor according to claim 22 characterized in that it comprises a binding moiety as the monoclonal antibody DC44 deposited under the deposition number 02060767 at the European

Collection of Cell Cultures (ECACC), Porton Down, Salisbury, UK.